REMARKS

I. STATUS OF THE CLAIMS

Claims 1, 3, 12-17, and 53-55 are pending. Claims 2, 4-11, and 18-52 are canceled without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications to the canceled subject matter.

II. OBVIOUSNESS REJECTION #1

Claims 53 and 54 are rejected under 35 U.S.C. § 103(a) over WO 96/33739 ("Garcon"). The Office asserts that Garcon teaches a composition comprising a negatively charged organic complex and a positively charged antigen. Office Action at page 3, first full paragraph. Garcon's antigen is an HSV glycoprotein, which is positively charged. *Id.* According to the Office, therefore, "Garcon *et al.* recognizes ... the addition of charges, negative, to stabilize the organic complex." *Id.* at page 3.

Applicants would point out that stabilizing an organic complex is not tantamount to promoting the electrostatic interaction and association between an antigen and an organic complex, as is presently recited. The person of ordinary skill in the art would understand that Garcon only suggests a way to make sturdy – *i.e.*, stabilized – liposomes. What Garcon says is that "liposomes may also contain a charged lipid which increases the stability of the liposome-QS21 structure for liposomes composed of saturated lipids" (page 2, lines 14-15). Garcon explains that "[i]n these cases the amount of charged lipid is preferably 1-20% w/w, most preferably 5-10%" (page 2, lines 15-17). Finally, Garcon teaches that "negatively charged liposomes" bind alum (page 11, lines 12-15), and that QS21, a saponin, may impose a negative charge on neutral liposomes (page 11, lines 18-20). This is the full extent of Garcon's disclosure concerning electrostatically charged vaccine components. Garcon does not teach or even contemplate increasing the negative charge of the liposome so that it is better equipped to attract and electrostatically bind a positively-charged antigen.

Thus, Garcon, when read in context, could not possibly have led the skilled artisan to modify the negative charge of Garcon's organic complex, thereby to promote

its electrostatic interaction with an antigen, the positive charge of which was increased correspondingly as well. Indeed, the Office admits at page 6 of the action that Garcon ***does not teach*** "increasing the positive charge of the antigen." At most, therefore, the skilled artisan would have learned that it *might* be desirable to increase the *stability* of Garcon's *liposomes* by incorporating charged lipids, and that inclusion of 5-10% w/w of charged lipids would be preferable in this regard. Garcon at page 2, lines 15-16.

In apparent recognition of this undeniable conclusion, and with all due respect, the Office appears to have misread or misconstrued Garcon's teachings in its attempt to find, or otherwise interject, some relevancy to the issue of electrostatic association. Since the only reasonable conclusion that the person of ordinary skill could draw from Garcon concerns its limited teaching about how to make liposomes stable, the Office attempts a semantical expansion of the phrase "electrostatic interaction" to underscore the rationale of this obviousness rejection.

But even Garcon's limited teaching regarding the stabilization of liposomes does not justify the Office's asserted rationale and in no way buttresses what is really a *post hoc* rationale for this rejection. None of this can deflect from the fact that Garcon conveys nothing about any sort of electrostatic interaction between the constituent components of Garcon's vaccine. Indeed, the Office itself "recognize[s] that Garcon et al. does not state explicitly that the organic complex and the antigen are electrostatically associated, as set forth in the claim." Office Action at page 7.

This understanding of Garcon alone supports Applicants' position that Garcon is irrelevant to the presently claimed invention and that that this rejection should be withdrawn. Applicants gather the Office realized that Garcon is off-point because the Office became obliged to advance the following, circuitous logic in order to redeem Garcon's pertinence to the pending claims. With respect, what the Office appears to have done is construe well-known terms of art in such a way to lend credence to Garcon. Thus, the Office's logic is that:

1. "entrapment or encapsulation of the antigen and organic complex allows the two components to associate with one another" (page 4, lines 7-8);

2. "according to Stedman's Medical dictionary, 'bound' is defined as limited, circumscribed, enclosed'" (page 4, lines 10-11);

3. therefore "[s]ince encapsulation involves enclosure of the antigen within the organic complex, the composition of Garcon *et al.* does comprise an antigen and an organic complex that are bound to one another" (page 4, lines 11-13); and that

4. hence, "Garcon et al. does teach a composition comprising an antigen and an organic complex that are 'electrostatically associated' with one another" (page 14, lines 15-17).

According to the Office, therefore, "entrapment" means "to associate," which means "bound to one another," which in turn means "electrostatically associated with one another." And "encapsulation" means "enclosed," which in turn means "bound." Thus, the logic is that liposomal entrapment literally means electrostatic association.

This solecism is logically unsupportable. This is not surprising, since it is simply a sequence of unsupported, conclusory statements that conflate (1) disclosures from Applicants' own specification, (2) an inappropriately expansive reading of Garcon's lipid-stabilization teaching, and (3) a medical dictionary definition for the word "bound." Moreover, this line of argument flies in the face of (4) the Office's admission that Garcon teaches neither antigen modification, to increase positive charge, nor anything about antigen : organic complex electrostatic interactions.

In relation to point (1), the Office is obliged to employ hindsight reconstruction , drawing from Applicants' specification in order to propound overlapping definitions between well-recognized terms of art. Thus, at page 4 of the action the Office states that Applicants "define[] 'electrostatically associated' as a reference to the organic carrier and the antigen being *linked, bound or otherwise associated* by means which includes

electrostatic interaction. [Paragraph bridging pages 9-10 of the specification]" (emphasis added).

So stating, the Office effectively misreads Applicants' own specification much in the manner of its misreading of Garcon. In particular, Applicants' reference to antigens and organic carriers that are "linked, bound or otherwise associated" in no way obviates the *required* presence of electrostatic interaction between the antigen and carrier. To the contrary, the paragraph bridging pages 9 and 10 of specification ends with the mandate that the *means* by which the antigen and carrier are "linked, bound or otherwise associated" must "include[] electrostatic interaction."

It is hardly surprising, therefore, that the specification makes no mention of a *non*-electrostatic means by which an antigen may be linked or bound to the organic carrier. More to the point, claims 53 and 54 explicitly *require* an electrostatic interaction ("said organic complex and said antigen are associated by an electrostatic interaction"). Electrostatic interactions between the antigen and carrier form the physical basis for the association between these components.

It is improper, therefore, for the Office to turn to a partial sentence in Applicants' specification to help re-define precise terms in such a way to buttress this prior-art rejection. At the very least, to do such a thing is a reflection of the Office's impermissible application of hindsight reconstruction. In this regard, the entire premise for the Office's obviousness rejection falls apart if Applicants' own teachings are extracted from the Office's semantic equation. A fresh reading of Garcon, *sans* knowledge of Applicants' claimed invention, would *not* have prompted one of skill in the art even to consider the possibility of electrostatically associating an antigen with an organic complex by way of their respective complementary charges. Thus, Garcon does not "relate to an immunogenic complex comprising a charged organic carrier and a charged antigen which . . . are electrostatically associated." See specification at page 2, lines 26-28.

Accordingly, Applicants submit that the Office has not met its burden to prove there exists a *prima facie* case of obviousness under Section 103(a), and even if that

burden has been met, the semantic basis for force-feeding Garcon into the parameters of the presently-claimed invention is improper and inappropriate. Nothing in Garcon would have prompted the skilled artisan to modify Garcon in such a way so as to arrive at the invention of claims 53 and 54. The skilled artisan might have modified liposome formulation in light of Garcon, as noted above, but that would be of no moment in the present context. Furthermore, the Office finds it "recognized that Garcon *et al.* does not explicitly state that the organic complex and the antigen are electrostatically associated, as set forth in the claim." Office Action at page 7. Certainly, the skilled artisan would have been of like mind and, hence, could not have arrived at a composition as presently claimed. For all of these reasons, therefore, Applicants respectfully request withdrawal of this rejection.

III. OBVIOUSNESS REJECTION #2

Claims 1, 3, 12-17 and 55 are rejected under 35 U.S.C. § 103(a), as allegedly unpatentable over Garcon, *supra*, in view of WO 98/36772 ("MacFarlan"). Office Action at page 5.

Applicants have explained why Garcon does not render claims 53 and 54 obvious. Garcon similarly does not render any of claims 1, 3, 12-17 or 55 as obvious either for the same reasons set forth in subsection II above. In fact, Applicants have established that Garcon is not a "primary reference" for purposes of supporting a Section 103 rejection. Since Garcon thus is irrelevant to the claimed invention, the application of MacFarlan is irrelevant, too. At the outset, therefore, Applicants therefore request withdrawal of this second obviousness rejection as well.

Nevertheless, Applicants take this opportunity to address what the Office has asserted with respect to MacFarlan and to explain why MacFarlan is inapplicable – even if there was some way to construe Garcon as applicable. The Office says that MacFarlan teaches "increasing the positive charge of peptides." Office Action at page 7. "Specifically, McFarlan [sic] teaches adding polyhistidine, which is positively charged, to the peptides." *Id.*

But this is not the complete story, however. MacFarlan is *not* about increasing the overall positive charge of a recombinant protein or polypeptide so as to facilitate an electrostatic interaction with an organic complex. Instead, MacFarlan is all about the use of *chelators* as the mechanism by which the protein or polypeptide can be associated with some other component. The word "electrostatic" does not even appear in MacFarlan. Hence, the title of the MacFarlan PCT application is "Chelating Immunostimulating Complexes." Thus, MacFarlan "is directed to incorporating into an immunostimulating complex matrix a recombinant protein or polypeptide incorporating a polyhistidine or other metal-chelating sequence allowing purification of the recombinant product by IMAC." MacFarlan at page 5, lines 6-11. MacFarlan's complex "is prepared in such a way that there is an exposed metal-chelating moiety able to spontaneously bind the recombinant product in the presence of appropriate metal ions." Id. at lines 13-17.

The very essence of MacFarlan, therefore, is a system that relies exclusively on chelation, whereby a coordination complex is formed by the bonding of a ligand to a central metal atom by coordinate covalent bonding. Thus, MacFarland's composition includes a metal-chelating moiety that binds a polypeptide that has at least one chelating amino acid sequence via a suitable metal ion. In MacFarlan's system, metal ions such as nickel ions, are bound to a chelating moiety, like iminodiacetic acid, which fully *neutralizes* the charge on the metal ions but leaves coordination sites available on the metal for electron sharing to occur. Coordination complexes therefore *differ* from electrostatic complexes because heavy metal ions are essential to MacFarlan's coordination complex, whilst they are unnecessary and irrelevant to electrostatic interactions, and because the ligand and receptor in a coordination complex are joined by covalent bonds – the antithesis of an electrostatic interaction. MacFarlan's system "attaches" a desired polynucleotide to the complex via chelation, whereby a metal ion links the two elements together.

Informed by these principals, and in light of the severe deficiencies in Garcon, the person of ordinary skill in the art would not have considered adding a negatively charged lipid "to the organic carrier of MacFarlan" in order to "enhance the stability of

the organic carrier," because the negatively charged lipid would utterly destroy MacFarlan's uncharged chelation-based system. Likewise, the skilled artisan would not have been prompted to modify Garcon to include MacFarlan's chelator moiety. No reasonable permutation of teachings gleaned from MacFarland and Garcon would have informed the person of ordinary skill about increasing the charges of an antigen or complex beyond its natural ionic charge, such that a complex is more negatively charged and an antigen is more positively charged than normal, promoting their electrostatic interaction.

For at least these reasons, the Office has not established a *prima facie* case of obviousness. The combination of Garcon (which is seriously defective) and MacFarlan (which has nothing to do with electrostatic interactions or associations), in no way renders claims 1, 3, 12-17 and 55 obvious. Applicants therefore respectfully request withdrawal of this obviousness rejection.

IV. DOUBLE PATENTING

Claims 53 and 54 are provisionally rejected on grounds of obviousness-type double patenting over claims of copending U.S. application serial No. 10/622,470. Office Action at page 10. Because the rejection is provisional, Applicants still defer any argument or "corrective" action until the Office allows claims in one of the copending applications.

CONCLUSION

Applicants request favorable reconsideration of the application. Should Examiner Le believe that any issue warrants further consideration, she is invited to contact the undersigned directly.

Respectfully submitted,

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The Commissioner is authorized to charge any additional fees, which may be required under 37 CFR §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, Applicants hereby petition for such extensions under 37 CFR §1.136 and authorize payment of the relevant fee(s) from the deposit account.